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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/925,122	Applicant(s) BANDMAN ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-15,17,20,23-26 and 44-59* is/are pending in the application.

4a) Of the above claim(s) *1-5,7,9-15,17,20,23-26,44,47,49,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 45-46, 48 and 50-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-5, 7-15, 17, 20, 23-26, 44-59 are pending.

2. Applicant's election with traverse of Group III, Claim 8 (now claims 8, 45-46, 48, 50-57) drawn to an antibody, composition comprising an antibody and a method of making antibody that read on species of polypeptide of SEQ ID NO: 1, filed 3/19/02, is acknowledged. The traversal is on the grounds that (1) the invention of newly added claims 44-59, drawn to antibodies and method of use could be examined at the same time without undue burden, (2) the instant claims antibodies directed to two polypeptide sequences and the claims examined should not be limited by an election of antibodies directed to only a single sequence and upon search and the examiner must extend the search of the Markush-type claim to include the non-elected species, which are antibodies directed to SEQ ID NO: 3 upon finding no art which antibodies directed to SEQ ID NO: 1. This is not found persuasive because (1) the polypeptides of SEQ ID NO: 1 and 3 differ with respect to their amino acid sequence and structure and antibody that binds specifically to one of the claimed sequences would not bind to the other sequence; (2) the newly added claims 11-13, 17, 20, 23-26, 44, 49, 58 and 59 are drawn to various methods such as screening, detecting, purifying and diagnosing using distinct products. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group III (now claims 8, 45-46, 48, 50-57) and Groups I-II, IV-XI and newly added claims 11-13, 17, 20, 23-26, 44, 49, 58 and 59 is still deemed proper and is therefore made FINAL.

3. Claims 1-5, 7, 9-15, 17, 20, 23-26, 44, 47, 49 and 58-59 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 8, 45-46, 48 and 50-57 drawn to antibody that bind to polypeptide of SEQ ID NO: 1 are being acted upon in this Office Action.

5. Claim 8 is objected to because it depends on non-elected claim 1.

6. Claim 48 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The "antibody is labeled" in claim 48 fails to further limiting the composition comprising the antibody in claim 46.

7. Applicant should amend the first line of the specification to update the relationship between the instant application and 09/294,545 filed 4/19/1999, which is now Pat No. 6,326,158.

8. The references cited on PTO 1449 filed 8/8/01 have been crossed out because none of the cited references have been submitted to the Office.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 8, 45-46, 48 and 50-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody which specifically binds to a purified polypeptide comprising an amino acid sequence of SEQ ID NO: 1 and 3 and (2) a method making said antibody for diagnostic assays, **does not** reasonably provide enablement for (1) *any* isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identical to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3; (2) *any* composition comprising *any* antibody mentioned above and an acceptable excipient for treating *any* disease; (3) *any* composition comprising *any* antibody mentioned above wherein the antibody is labeled, (4) A method of preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1

and 3; (5) A method of preparing a monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3; (6) *any* monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3, (7) *any* composition comprising *any* monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3, (8) *any* monoclonal antibody mentioned above and a suitable carrier for treating *any* disease, (9) *any* antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for treating *any* disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method of how to make and use a polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody for diagnostic and detection assays (See page 31-32).

The specification does not teach how to make and use *any* antibody that binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide "having" the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide "having" an amino acid sequence of SEQ ID NO: 1 and 3 since neither the structure nor function of *any* amino acid sequence mentioned above is provided. Furthermore, the term "having" is open-ended. It expands the polypeptide fragment to include additional amino acid residues at either end. Given the indefinite number of undisclosed amino acid sequence and polypeptide fragment thereof, there is insufficient guidance in the specification as to the structure associated with functional properties of said polypeptide, biochemical information such as the specific amino acids residues used as an immunogen, epitopes and antibody binding specificity, it is unpredictable that immunizing with an undisclosed amino acid sequence and polypeptide fragment will have the same antibody specificity as the antibody that binds specifically to SEQ ID NO: 1 and 3, in turn, would be useful for any purpose.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable to determine which antibody generated from a naturally-occurring amino acid sequence such as having 90% sequence identity to SEQ ID NO: 1 and 3 or fragment thereof "having" an amino acid sequence of SEQ ID NO: 1 and 3will have the same antibody specificity as an antibody generated from the full-length polypeptide selected from the group consisting of the amino acid sequence of SEQ ID NO: 1 and 3. Since the amino acid sequence and specificity of said antibody is not enabled, it follows that

the method of making any antibody using any undisclosed amino acid sequence, biologically active fragment of the polypeptide and any immunogenic fragment "having" the amino acid sequence of SEQ ID NO: 1 and 3 is not enabled.

With regard to composition comprising any polyclonal or monoclonal antibody with the specificity mentioned above and an acceptable excipient or suitable carrier, the specification fails to provide any *in vivo* working examples, or guidance with respect to treating a patient suffering from *any* specific disease using *any* antibody mentioned above. Given the indefinite number of disease, the lack of guidance and in vivo working examples, further research is required. Since the composition comprising said antibody is not enabled, it follows that composition comprising the labeled antibody is not enabled.

The '370 patent teaches that the inherent problem with chimeric antibody has been a loss of affinity for the antigen, which means more antibody will have to be injected into a patient at higher cost and greater risk of adverse effects such as serum sickness (See column 2 lines 12-27, in particular). In the absence of in vivo working examples, it is unpredictable for the following reasons: (1) the antibody may be inactivated before producing an effect, i.e. such as inherently short half-life of the antibody; (2) the antibody may not reach the target area; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as serum sickness which prohibitive to the use of antibody for such treatment. Therefore, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 8, 45-46, 48, and 50-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identical" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide "having" an amino acid sequence of SEQ ID NO: 1 and 3; (2) *any* composition comprising *any* antibody mentioned above and an acceptable excipient for "treating *any* disease"; (3) *any* composition comprising *any* antibody mentioned above wherein the antibody is labeled, (4) A method of preparing a polyclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3; (5) A method of preparing a monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3; (6) *any* monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3, (7) *any* composition comprising *any* monoclonal antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence "having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3, (8) *any* monoclonal antibody mentioned above and a suitable carrier for treating *any* disease, (9) *any* antibody with the specificity of an isolated antibody which specifically binds to a polypeptide comprising a) *any* naturally-occurring amino acid sequence

"having at least 90% sequence identity" to the amino acid sequence of SEQ ID NO: 1 and 3, b) *any* biologically active fragment of the polypeptide having the amino acid sequence of SEQ ID NO: 1 and 3, c) *any* immunogenic fragment of the polypeptide having an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is produced by screening a Fab expression library or a recombinant immunoglobulin library for treating *any* disease.

The specification discloses only a method of how to make and use a polyclonal, monoclonal, chimeric, humanized antibody which specifically binds to a polypeptide consisting of an amino acid sequence of SEQ ID NO: 1 and 3 wherein the antibody is a chimeric antibody, a single chain antibody, a Fab fragment, a F(ab')2 fragment thereof or a humanized antibody for diagnostic and detection assays (See page 31-32).

With the exception of the specific antibody that binds to a polypeptide consisting of SEQ ID NO: 1 and 3, there is insufficient written description about the structure associated with function of an isolated antibody that binds to (1) *any* naturally-occurring amino acid sequence "having" at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 1 and 3, (2) *any* biologically active fragment of the polypeptide "having" the amino acid sequence of SEQ ID NO: 1 and 3, (3) *any* immunogenic fragment of the polypeptide "having" an amino acid sequence of SEQ ID NO: 1 and 3 for in vivo treatment of any disease and diagnostic assays. The term "having" is open-ended. It expands the fragment to include additional amino acids at either end. Further, there are no additional representative species of polypeptide other than the polypeptide of SEQ ID NO: 1 and 3 to which the antibody binds wherein the antibody is polyclonal, monoclonal, chimeric, humanized, Fab fragment, F(ab')2 fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 8 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, page 93).

Chan *et al* teach a biologically active or immunogenic fragment of FBP17 such as residues TCP to PTSYV comprising an amino acid sequence at least 90% identical to the claimed biologically active or immunogenic fragment polypeptide of SEQ ID NO: 1 (residues 198-244 of SEQ ID NO: 1) (See Fig 3A, in particular). Further, Chan *et al* teach a biologically active or immunogenic fragment such as APPTPPPLPP (page 1046, Fig 1, 1048, column 1, first paragraph, in particular) and the reference fragments functionally resemble SH3 domain, which is useful for regulating limb and kidney development (See page 1045, in particular).

The claimed invention as recited in claim 8 differs from the reference only by the recitation that an isolated antibody which specifically binds to a biologically active fragment or an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO: 1 or to a biologically active fragment or an immunogenic fragment of a polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO: 1.

The claimed invention as recited in claims 50-51 differs from the reference only by the recitation that a method of preparing a polyclonal antibody with the specificity mentioned above.

The claimed invention as recited in claim 52 differs from the reference only by the recitation that a composition comprising a polyclonal antibody with the specificity mentioned above and a suitable carrier.

Harlow *et al* teach a method of producing polyclonal antibody to any antigen (See page 93, in particular). Harlow *et al* further teach that for practical reasons, rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified. Harlow *et al* teach a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce polyclonal antibody as taught by Harlow *et al* with the polypeptide fragments as taught by Chan *et al* for a composition comprising an antibody and a carrier as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach rabbits represent a good choice for the routine production of polyclonal sera since they are easy to keep and handle and antibody produced are well characterized and easily purified (See page 93, in particular). Chan *et al* teach that the reference FBP17 polypeptide fragment is most homologous to the SH3 domain that binds to the consensus proline rich sequences such as APPTPPPLPP (page 1048, column 1, first paragraph, in particular) and functionally resemble SH3 domain which is useful for regulating limb and kidney development (See page 1045, in particular).

15. Claims 45, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 319-356, and 626-629).

The teachings of Chan *et al* have been discussed supra.

The claimed invention as recited in claim 45 differs from the reference only by the recitation that the antibody is a Fab fragment, a F(ab')2 fragment.

The claimed invention as recited in claim 46 differs from the reference only by the recitation of a composition comprising said antibody and an acceptable excipient.

The claimed invention as recited in claim 48 differs from the reference only by the recitation the antibody is labeled.

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular). Harlow *et al* further teach labeling any antibody with various labels such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354, in particular) or NaCl, which is a saline solution (See page 346, in particular) for various detection assays. The advantages of enzyme labeling are longer shelf life, and higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibody fragment such as Fab or F(ab')2 or to label any antibody as taught by Harlow *et al* with the polyclonal antibody that binds specific to the polypeptide fragment as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow *et al* teach antibody fragments can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular) and the labeled antibody can be used for various detection assays. The advantages of enzyme labeling

are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

16. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 4,946,778 (Aug 1990, PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a single chain antibody.

The '778 patent teaches a method of producing single chain antibody comprising a variable region of any antibody or a polypeptide fragment (See column 29, lines 25 bridging column 30, lines 1-20, in particular). The advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to make single chain antibody as taught by the '778 patent that binds specifically to the polypeptide fragment as taught by the Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '778 patent teaches the advantages of a single chain antibody are small size, greater stability, significantly reduced cost and could be engineered to be highly antigenic and yet reduce the body's immunologic reaction and thus increase the safety and efficacy of the therapeutic application (See column 3, lines 33-48, in particular).

17. Claims 45, 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of US Pat No. 6,180,370B, filed June 1995; PTO 892).

The teachings of Chan *et al* have been discussed supra.

The claimed invention in claim 45 differs from the reference only by the recitation that the antibody is a chimeric antibody, a humanized antibody.

The claimed invention in claim 56 differs from the reference only by the recitation that the antibody is produced by screening a Fab expression library.

The claimed invention in claim 57 differs from the reference only by the recitation that the antibody is produced by screening a recombinant immunoglobulin library.

The '370 patent teaches a method of producing chimeric antibodies (See column 55 lines 25-59; column 59, lines 65, in particular) and humanized antibodies (See column 44 line 33; column 68 lines 8-44, in particular) by screening a Fab expression library or a recombinant immunoglobulin library. The reference chimeric antibody comprising a variable region of an antibody and a human immunoglobulin constant region. The '370 patent further teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce chimeric antibody or humanized antibody as taught by the '370 patent that binds specifically to the polypeptide fragment as taught by Chan *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '370 patent teaches that the chimeric humanized immunoglobulins (antibodies) specifically reactive with strong affinity to a predetermined antigen and remain nonimmunogenic in humans yet be easily and economically produced in a manner suitable for therapeutic formulation and other uses (See column 2, lines 29-34, in particular).

18. Claims 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan *et al* (EMBO J 15(5): 1045-54, 1996; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-149).

The teachings of Chan et al have been discussed supra.

The claimed invention as recited in claim 53 differs from the reference only by the recitation that a method of making monoclonal antibody.

The claimed invention as recited in claim 54 differs from the reference only by the recitation of a monoclonal antibody produced by the method of claim 53.

The claimed invention as recited in claim 55 differs from the reference only by the recitation a composition comprising the monoclonal antibody and a suitable carrier.

Harlow *et al* teach a method of producing monoclonal antibody (See page 139-149, in particular) and the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular). Harlow *et al* further teach labeling any antibody with various label such as enzyme or FITC (See chapter 9, in particular) in a composition comprising an antibody and a carrier such as PBS (See page 354 in particular) or NaCl, which is a saline solution (See page 346) for various detection assays. The advantages of enzyme labeling are longer shelf life, higher sensitivity while the advantages of fluorochrome label are long shelf life and good resolution in immunohistochemistry (See page 322, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce monoclonal antibody as taught by Harlow *et al* with the polypeptide fragment as taught by Chan *et al* for a composition comprising said antibody and a carrier such as PBS as taught by Harlow *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody fragment because Harlow *et al* teach that the advantages of monoclonal antibodies are their specificity of binding, their homogeneity and their ability to be produced in unlimited quantities (See page 141, last full paragraph, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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